Enantioselective Synthesis of a Tetrasubstituted Oxocane via a Double Diastereoselective Hetero Diels-Alder Reaction

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Abstract: A procedure for the enantioselective preparation of tetrasubstituted medium sized cyclic ethers is presented. An oxocane is prepared by a sequence which involves a double diastereoselective hetero Diels-Alder reaction between a chiral aldehyde and a diene bearing an allylic chiral centre. The cycloadduct is transformed into a linear ether which is then converted to the cyclic ether by a highly regioselective intramolecular alkylation of a lithiosulfone with an epoxide. The sense of induction of the chiral centre on the diene is discussed.

Key words: hetero Diels-Alder reaction, double diastereoselectivity, intramolecular alkylation, cyclic ethers

Medium sized cyclic ethers, substituted at the positions adjacent to the oxygen atom (α, α',β, β') have attracted considerable interest because they constitute the basic skeleton of many metabolites isolated mainly from marine sources,[1] and also because they are the basic units of the important fused polyether marine toxins.[2] In these latter compounds, the most usual relative stereochemistry of the substituents in each of the fused cyclic ethers is *trans*, *syn*, *trans* (Figure 1).

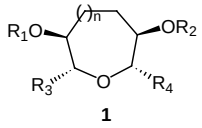

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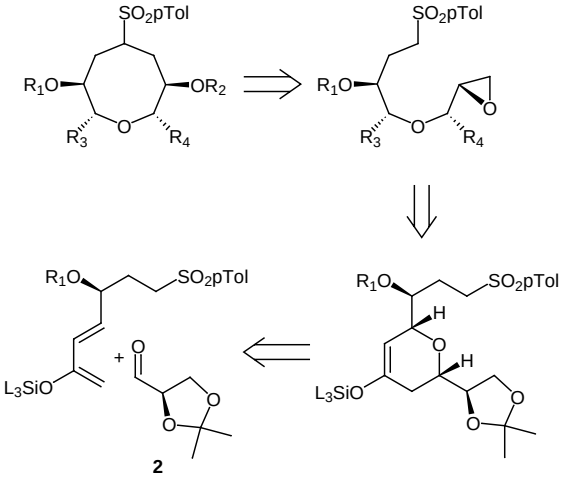
Figure 1

We have recently reported on a methodology for the enantioselective preparation of medium sized, bi- and trisubstituted cyclic ethers using an intramolecular alkylation of a lithiosulfone with an epoxide.[3] The control over the relative stereochemistry of the substituents is attained by the use of a hetero Diels-Alder reaction between a monoactivated diene and a chiral aldehyde.

In this communication we present the extension of this methodology to the preparation of cyclic ethers tetrasubstituted at the α, α', β, and β' positions. Scheme 1 shows a retrosynthetic scheme for the preparation of a tetrasubstituted oxocane, based on the methodology previously used for trisubstituted systems. For this scheme to be successful, the intramolecular cyclization reaction has to be highly regioselective, a result that can be expected based on our previous experience with similar compounds.[3b]



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Scheme 1

Since the introduction of the fourth substituent in the molecule requires its placement at the allylic position of the diene, another important point to consider is the sense of induction of both components in the key hetero Diels-Alder reaction. To obtain an acceptable yield and selectivity, both fragments must work in the same direction, that is, it must be a matched double diastereoselective reaction. The sense of induction of the chosen (*R*)-(+)-**2** aldehyde is well known,[4] following Cram's rule with high *endo* selectivity (*endo*:*exo* 7:1 in our previous work with non-chiral dienes[3b]). The induction exerted by an allylic chiral centre in a linear diene, however, is not that well understood, giving rise, in the cases reported,[5] to products coming from the approach of the dienophile through either face of the diene (*like* or *unlike* approaches[6]). The selectivity seems to depend on several factors, such as the nature of the dienophile and the substitution pattern on the diene.[5] The number of examples of chiral dienes acting in a hetero Diels-Alder reaction with aldehydes as dienophiles is scarce, but in a system closely related to ours, Wu et al.[7] observed a major product coming from the *unlike* approach of ethyl glyoxylate to the diene. The face selectivity due exclusively to the dienic chiral centre seems to be low in the absence of other chiral partners such as chiral Lewis acids or dienophiles.

According to our modelization of the reaction, in order to obtain the required stereochemistry (Scheme 1), the approach of the dienophile to the diene must occur as shown in Figure 2. The (*R*)-(+)-**2** aldehyde approaches the diene

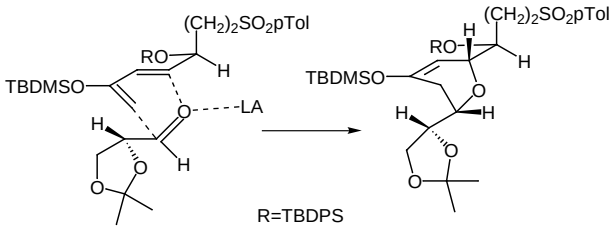
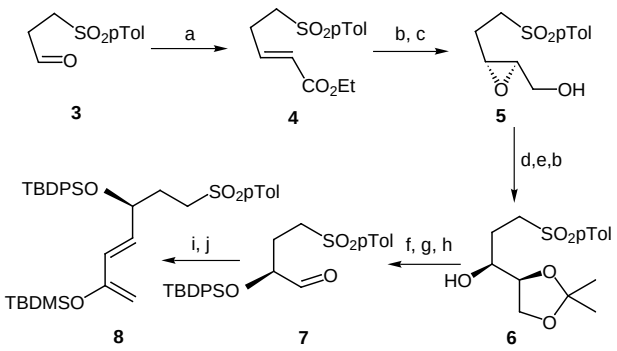


Figure 2

through its less hindered face with the alkoxy group situated at the "inside" position and the alkyl group almost perpendicular to the plane of the diene and away from the incoming aldehyde[8] (this makes the approach *unlike*). The Lewis acid coordinated to the oxygen atom is located in the *exo* position[9] and *trans* to the acetonide, making the approach *endo*-Cram to the carbonyl. In this transition state, all steric repulsions are minimized, and the stereochemical outcome of the reaction should provide the required *trans*, *syn*, *trans* relative dispositions of the groups around the oxygen atom of the ether.

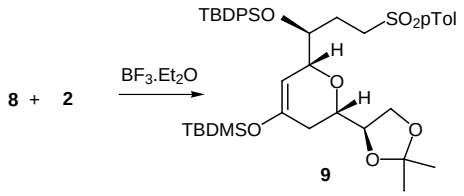


a) $EtO_2CCH_2P(O)(OEt)_2$, HNa, THF, 0ºC (74%); b) DIBALH, Et_2O, -70ºC (90%); c) Ti(OPr-i)$_4$, (-)-DIPT, ^{t}BuOOH, CH_2Cl_2, Molecular sieves 3Å (84%); d) Ti(OPr-i)$_4$, $PhCO_2H$, CH_2Cl_2, (73%); e) DMP, DMSO, pTsOH, (e+b, 98%); f) TBDPSCl, Imidazole, CH_2Cl_2, (92%); g) CSA, MeOH, 0ºC (78%); h) $NaIO_4$, nBu_4NIO_4, MeOH, H_2O; i) $CH_3COCH_2P(O)(OEt)_2$, NaH, THF, 0ºC (85%, 2 steps); j) TBDMSOTf, Et_3N, 0ºC to r. t. (84%).

Scheme 2

In order to check the viability of our retrosynthetic analysis, and whether the reaction proceeds with the required sense of induction, we decided to carry out the synthesis of an oxocane skeleton, and for this the diene needs to have a three carbon chain (Scheme 1). The required diene was prepared as shown in Scheme 2. Aldehyde **3**[3b] was transformed into an allylic alcohol by the sequence: Wittig-Horner reaction, yielding **4**, and reduction with DIBALH. The asymmetric induction was performed by a Sharpless asymmetric epoxidation reaction[10] which gave **5** in greater than 95% yield.[11] Epoxide **5** was then opened with benzoic acid and Ti(OPr-i)$_4$.[12] The resulting diol was protected as the acetonide, and the benzoate was removed by reduction followed by protection of the hydroxyl as the *tert*-butyldiphenylsilyl ether. Deprotection of the acetonide and cleavage of the diol with $NaIO_4$ gave aldehyde **7**, which was transformed into an α, β-unsaturated ketone via a Wittig-Horner reaction. Formation of the *tert*-butyldimethylsilyl enol ether afforded the desired diene **8**.

The hetero Diels-Alder reaction of diene **8** and *(R)*-(+)-**2** was carried out under similar conditions to those employed in our previous work,[3] using 1.5 equivalents of $BF_3{\cdot}Et_2O$ as Lewis acid and diethyl ether as solvent. The control of the temperature was critical in achieving good selectivity, since at low temperature the reaction was very slow and part of the diene reverted with time to the corresponding α, β-unsaturated ketone. At higher temperature, the selectivity was lower although the reaction proceeded in a few minutes. The best results were obtained at −15 ºC, at which point only one cycloadduct, **9**, was obtained in 74% yield after 15 minutes (Scheme 3). Part of the starting material was recovered in the form of the α, β-unsaturated ketone.

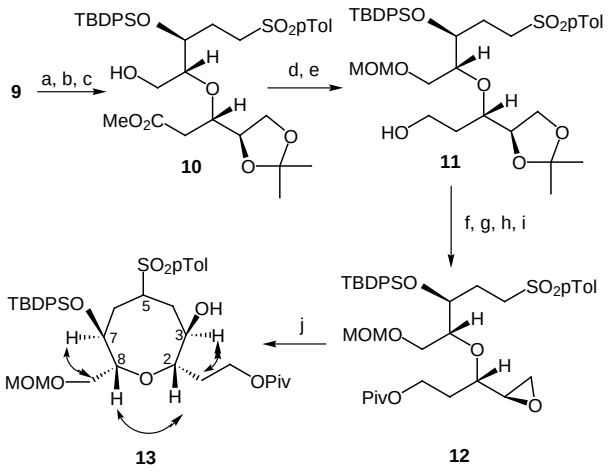


Scheme 3

The high selectivity and good yield of the reaction seems to indicate that the reactants used are the matched pair of the double diastereoselective reaction. At this point, it was difficult to establish the configuration of the newly created chiral centres due to the unstable nature of the adduct, but since our goal was to prepare a cyclic ether, we decided to continue the synthesis and verify the stereochemistry in the final product. From our experience, the relative disposition of the substituents in the cyclic ether can be easily assigned by using nOe experiments. The transformation of the adduct **9** into the oxocane **13** was carried out as shown in Scheme 4. The transformations depicted in Scheme 4 are similar to those used in our previous work,[3] except that in this synthesis, each hydroxyl was protected with a different group to differentiate them and allow further elaboration of the final product, for instance to prepare a polycyclic compound. The cyclization step was carried out in THF at −65 ºC using 4 equivalents of LDA, yielding 71% of the desired compound **13** with an oxocane skeleton, as a single isomer, as determined by a spectroscopic analysis.[13]

The nOe data (ROESY and noediff experiments) showed the correlations indicated in Scheme 4 for **13**, clearly indicating that the relative stereochemistry is the expected *trans*, *syn*, *trans*, and that the cycloaddition step took place as anticipated through the combination of *endo*-

Cram approach to the aldehyde and *unlike* approach to the diene. It was not possible, however, to determine the stereochemistry at the carbon atom bearing the sulfone group due probably to the conformational flexibility of that part of the molecule.



a) O_3, CH_2Cl_2, MeOH; b) $NaBH_4$; c) CH_2N_2, Et_2O (87% three steps); d) MOMCl, $^iPr_2NEt$, 0ºC to r.t. (98%); e) DIBALH, Et_2O, -60ºC (94%); f) $(CH_3)_3COCl$, Py, 0ºC to r.t. (98%); g) CSA, MeOH, 0ºC to r.t. (84%); h) TsCl, DMAP, Et_3N, CH_2Cl_2; i) NaH, THF (85%, two steps); j) LDA, THF, -65ºC (71%).

Scheme 4

The work reported herein demonstrates that medium sized tetrasubstituted cyclic ethers can be prepared in enantiomerically pure form through the synthetic scheme proposed, making use of the double diastereoselective Diels-Alder reaction. The opposite absolute stereochemistry can be achieved by the use of the easily obtained enantiomers of the aldehyde and diene. This work also presents new evidence on the tendency of dienes bearing an allylic chiral centre to react with aldehydes in an *unlike* manner.

Acknowledgement

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(13) Procedure for the cyclization reaction: To a solution of 22 mg (0.03 mmol) of **12** in 6 mL of THF at −65 ºC, were added 0.5 ml of a solution of LDA (0.24 M, 4 equiv.) in THF. When no further progress was observed by TLC (15 min), 1 mL of saturated aqueous solution of NH_4Cl was added and the reaction was allowed to reach room temperature. After extraction with ether, concentration and flash column chromatography (25% EtOAc in hexanes), 15.6 mg of **13** were obtained as a clear oil (71% yield). Data for **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H, ^{t}Bu), 1.17 (s, 9H, ^{t}Bu), 1.65-1.72 (m, 1H, -CH_2-CH_2OPiv), 1.82-1.94 (m, 2H, -CH_2-CH_2OPiv, H6), 2.12 (dd, 1H, *J* = 8.4, 14.6 Hz, H4), 2.39-2.52 (m, 2H, H4', H6'), 2.44 (s, 3H, CH_3-$ArSO_2$-), 2.95 (dd, 1H, *J* = 6.7, 10.3 Hz, -CH_2-OMOM), 3.01 (dd, 1H, *J* = 4.3, 10.3 Hz, -CH_2-OMOM), 3.10 (s, 3H, CH_3-O-), 3.52-3.55 (m, 1H, H8), 3.68-3.72 (m, 1H, H2), 3.76-3.81 (m, 1H, H5), 3.88 (t, 1H, *J* = 5.9 Hz, H3), 4.02 (dd, 1H, *J* = 2.7, 2.7 Hz, H7), 4.08-4.12 (m, 2H, -CH_2OPiv), 4.28 (s, 2H, O-CH_2-O), 7.28-7.70 (m, 14H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1 (s), 21.5 (q, CH_3Ar), 26.9 (q, ^{t}Bu), 27.1 (q, ^{t}Bu), 29.9 (t, C6), 32.2 (t, C4), 33.2 (t, CH_2CH_2OPiv), 38.6 (s), 55.0 (q, CH_3-O), 55.3 (d, C5), 61.1 (t, -CH_2OPiv), 68.6 (t, CH_2-OMOM), 72.3 (d, C3), 72.5 (d, C7), 80.7 (d, C2), 82.7 (d, C8), 96.2 (t, O-CH_2-O), 127.8 (d, Ar), 129.7 (d, Ar), 130.0 (d, Ar), 130.1 (d, Ar), 132.1 (s, Ar), 132.5 (s, Ar), 134.6 (s, Ar), 135.8 (d, Ar), 144.4 (s Ar), 178.5 (s, C=O).

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